DISSERTATION ON COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE WITH CLONIDINE AND EPIDURAL BUPIVACAINE IN ORTHOPAEDIC LOWER LIMB SURGERIES

Dissertation submitted to

TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

Chennai

for

MD (ANAESTHESIOLOGY) Branch - X

March 2009

GOVT. STANLEY MEDICAL COLLEGE

Chennai

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – TAMIL NADU

CERTIFICATE

This is to certify that this dissertation entitled dissertation on **"COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE WITH CLONIDINE AND EPIDURAL BUPIVACAINE IN ORTHOPAEDIC LOWER LIMB SURGERIES"** is the bonafide original work of **Dr.K.KARTHIK,** in partial fulfillment of the requirement for MD anaesthesiology examination of the **Tamilnadu Dr. MGR Medical University** to be held in March 2009.

Prof. Dr. J. Mohanasundaram
M.D. Phd. D.N.B.
DEAN,
Govt. Stanley Medical College & Hospital,
Chennai-600 001.

Prof.Dr.P.Chandrasekar
M.D. D.A.,
Head of the department
Department of Anaesthesiology,
Govt. Stanley Medical College & Hospital, Chennai-600 001.

DECLARATION

I, Dr.K.KARTHIK, solemnly declare that dissertation titled, Dissertation on **"COMPARISON OF POST OPERATIVE ANALGESIA FOLLOWING EPIDURAL BUPIVACAINE WITH CLONIDINE AND EPIDURAL BUPIVACAINE IN ORTHOPAEDIC LOWER LIMB SURGERIES"** is the bonafide work done by me at Govt.Stanley medical college and hospital during the period January 2008 to August 2008 under the expert guidance and supervision of Prof. Dr. P. Chandrasekar M.D. D.A.

The dissertation is submitted to the Tamilnadu Dr. MGR Medical university towards partial fulfillment of requirement for the award of MD Degree in anaesthesiology.

Place : Chennai

Date : **Dr. K. KARTHIK**

ACKNOWLEDGEMENT

I am extremely thankful to **PROF.DR.J. MOHANASUNDARAM MD, Phd, DNB, Dean**, Stanley Medical College, Chennai for permitting me to do this study in our Institution.

I take this opportunity to express my heartfelt gratitude to **PROF. DR. P. CHANDRASEKAR, MD,DA.**, Professor and head of the department of anaesthesiology, Stanley Medical College, Chennai, for his keen interest, constant encouragement, guidance and valuable suggestions throughout this study.

I am extremely thankful to **PROF. DR. B. KALA, M.D,D.A.**, Professor of Anesthesiology,Stanely Medical College,Chennai, who has extented her unstinted encouragement, guidance and valuable suggestiosS during the study.

My sincere thanks to **PROF. DR. R. MATHAN KUMAR, M.D, D.A.**, Professor of Anesthesiology, Stanely Medical College, Chennai, for the encouragement and guidance extended to me during the study.

My Sincere thanks to **PROF.DR. S. GUNASEKAR, M.D, D.A., D.N.B**, Professor of Anesthesiology, Stanely Medical College, Chennai, for the encouragement and guidance extended to me during the study.

I am extremely thankful to **DR. N. BASKER, M.D,** Asst. Professor, Department of Anesthesiology, for his guidance.

I thank **ALL ASSISTANT PROFESSORS** who evinced keen interest and gave support without which this study would not have been possible.

I thank **Mr. PADMANABAN**, Statistician, for helping me in the statistical analysis.

I thank all Post graduates for their valuable support during the study period.

I thank all theatre personnel for their co-operation.

I thank all patients without whose participation, this study would not have been possible.

CONTENTS

INTRODUCTION

Recent advances in neurosciences have demonstrated that peripheral tissue injury may lead to long alterations in central processing with reduction in pain threshold, amplification of response to pain. Comparable alterations may also occur following surgical trauma, resulting in amplification and prolongation of postoperative pain.

Postoperative pain treatment should be an integral component of the routine surgical and anaesthetic management not only for humanitarian reasons but also because it can help to reduce morbidity and complications as well as accelerate rehabilitation .Good perioperative analgesia is an important avenue to attenuate the surgical stress response

Post operative pain relief can be provided by pharmacological and non-pharmacological methods. Non pharmacological methods include hypnosis, cold or heat, relaxation therapy, splinting of wounds, Transcutaneous Electrical Nerve Stimulation and pre-operative explanation and education. The pharmacological methods include simple analgesics, Non- steroidal anti- inflammatory drugs, Opioids (oral, intramuscular, intravenous, Patient Controlled Analgesia, Epidural or intrathecal) and Local anaesthetic agents (wound infiltration, nerve blockade, epidural, intrathecal).

Epidural anaesthesia is a central neuraxial block technique with many applications. Epidural anaesthesia can be used as sole anaesthetic for procedures involving the lower limbs, pelvis, perineum and lower abdomen . The advantage of epidural over spinal anaesthesia is the ability to maintain continuous anaesthesia after placement of an epidural catheter, thus making it suitable for procedures of long duration. This feature also enables the use of this technique into the postoperative period for analgesia, using lower concentrations of local anaesthetic drugs or in combination with different agents.

Clonidine an alpha – 2 agonist drug, which was introduced into clinical practice as an anti-hypertensive medication, can be used as an additive to local anaesthetics in nerve blockade and central neuraxial blockade. Following local anaesthetics and opioids, clonidine is the most studied drug used for human neuraxial analgesia. Although the systemic administration of clonidine can provide analgesia, its primary site of antinociceptive action appears to be at the spinal level. Alpha - 2 receptors at the spinal cord level are thought to be responsible for the analgesic properties of α2-adrenergic agonists (10,11).

This study was designed to evaluate the analgesic efficacy of bupivacaine and clonidine mixture given through lumbar epidural route in patients undergoing elective orthopaedic lower limb surgeries ,comparing the quality of analgesia with

epidural plain bupivacaine and also to calculate the number of post-operative aanalgesic doses required.

AIMS AND OBJECTIVES

1. To evaluate the analgesic efficacy of bupivacaine and clonidine mixture given through lumbar epidural route for postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries, by calculating the number of doses of postoperative analgesics required.

2. To compare the quality and duration of analgesia of epidural bupivacaine - clonidine mixture with epidural plain bupivacaine intra and post- operatively.

3. To evaluate the hemodynamic response of epidural clonidine intra and post-operatively.

DEFINITION OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."

PHYSIOLOGY OF PAIN

Nociception is conveyed from the periphery to the brain at three levels:the peripheral nociceptor, the spinal cord, and the supra-spinal (brain) levels(1).

There are two types of pain- Physiological and Pathological.

I . PHYSIOLOGICAL PAIN :is produced by stimulation of high threshold thermo/mechanical nociceptors, which transmit via fast conducting myelinated A delta fibres. These enter the dorsal horn of the spinal cord and synapse at laminae I and V.

II . PATHOLOGICAL PAIN: originates from stimulation of the high threshold polymodal nociceptors (free endings) present in all tissues. The nociceptors respond to mechanical, chemical and thermal stimuli and are transmitted via slow conducting unmyelinated C fibres. These synapse at

laminae II and III (substantia gelatinosa) of the dorsal horn. The second order neurons are either nociceptive specific (substantia gelatinosa) or wide dynamic range (WDR) neurons (in laminae V and VI) that respond to a wide range of noxious and non-noxious input. Both pathways ascend up the spinal cord via the spinothalamic tracts to the thalamus, which synapse and project on to the somatosensory cortex. Inhibitory inter-neurons in the substantia gelatinosa prevent activation of the dorsal root ganglia. Interneurons can be activated by A beta and inhibited by A beta and C fibre activity. Pain can be gated-out by stimulating the large A beta fibres in the painful area. This is the working mechanism behind transcutaneous electrical nerve stimulation. The descending inhibition pathways originate at the level of the cortex and thalamus, and descend via the brainstem (periaqueductal grey) and the dorsal columns to terminate at the dorsal horn of the spinal cord. Neurotransmitters noradrenaline, serotonin (5-HT) and the endogenous opioids are released to provide antinociception

POST OPERATIVE PAIN

Effects of postoperative pain:

Postoperative pain can affect all organ systems and includes

Cardiovascular - increased myocardial oxygen consumption which may lead to ischemia.

Respiratory - reduced cough, atelectasis, sputum retention and hypoxemia.

Gastrointestinal - delayed gastric emptying, reduced gut motility and constipation.

Genitourinary - urinary retention.

Neuroendocrine - hyperglycemia, protein catabolism and sodium retention.

Musculoskeletal - reduced mobility, pressure sores and increased risk of deep vein thrombosis.

Psychological - anxiety and fatigue.

Benefits of epidural analgesia

Use of postoperative epidural anaethaesia and analgesia especially with a local anaesthetic – based analgesic solution can attenuate the pathophysiologic response to surgery and may be associated with a reduction in mortality and morbidity compared with analgesia with systemic opioids.

Rodgers et al(19) demonstrated through a meta-analysis of randomized data that perioperative use of neuraxial anaesthesia and analgesia versus general anaesthesia and systemic opioids reduced overall mortality by approximately 30%. Use of epidural analgesia can decrease the incidence of postoperative gastrointestinal, pulmonary and cardiac complications.

Christopherson et al(6) demonstrated that use of intra operative regional anaesthesia reduced hypercoagulable – related events (eg. Deep vein thrombosis, pulmonary embolism, vascular graft failure).

Postoperative analgesia in orthopaedics

Postoperative pain is of major concern after orthopaedic lower limb surgery. Moderate to severe at rest, it is exacerbated on movement and particularly after hip and knee surgery and by severe reflex muscular spasm. This not only causes patient discomfort but also compromises the early physical therapy, the most influential factor on rapid postoperative rehabilitation and ambulation.

Postoperative pain relief can be achieved by a number of techniques such as intravenous patient controlled analgesia (PCA) with morphine or nonsteroidal anti-inflammatory drugs or epidural analgesia. Effective analgesia with epidural or peripheral block reduces narcotic requirements, provides better analgesia, reduces catabolism and results in improved rates of rehabilitation after orthopeadic lower limb surgeries.

The benefits of effective postoperative analgesia in orthopeadic surgeries was made evident by the fact it facilitates early ambulation which is beneficial in the prophylaxis of deep vein thrombosis, which is a common problem encountered in orthopaedics(20). Postoperative modalities like pneumatic compression boots, foot pumps, foot exercises and aspirin can be safely used in conjunction with epidural anaesthesia to reduce the incidence of deep vein thrombosis.

BUPIVACAINE

Bupivacaine was introduced by Boaf Ekenstam in **1963**

Chemical structure: bupivacaine hydrochloride is 2-piperidenecarboxamide 1-butyl-N-(2,6 dimethylphenyl) monochloride, a monohydrate is a white crystalline powder that is freely soluble in 95% ethanol soluble in water and slightly soluble in chloroform or acetone.

It has the following structural formula:

Bupivacaine is related chemically and pharmacologically to the amide group of local anesthetics. It is structural homologues of mepivacaine.

Presentation: bupivacaine hydrochloride is available in sterile isotonic solution with or without epinephrine 1:2,00,000 for injection. 0.25%,0.5%,0.75% concentration containing 2.5mg/dl, 5mg/dl, 7.5mg/dl of bupivacaine hydrochloride respectively. Sodium chloride, sodium hydroxide ± hydrochloric acid for pH adjustment. Methylparaben 1mg/ml added as preservative.

0.5%(hyperbaric) solution contain 80mg/ml of glucose(with a specific gravity of 1.026) - for intrathecal use.

Mechanism of action:

Local anaesthetics diffuse in their nonionized form through neural sheaths and the axonal membrane to the internal surface of the cell membrane sodium ion channels where they combine with hydrogen ions to form a cationic species which enters the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channels thereby decreasing sodium conductance and preventing depolarization of the cell membrane.

Pharmacological action:

a) Central nervous system(CNS):the principle effect of bupivacaine is reversible neural blockade, this leads to a characteristically biphasic effect on the CNS.

- Initially excitation: light headness, dizziness, visual and auditory disturbances and seizures occurs due to blockade of inhibitory pathways in cortex.
- With increasing doses: CNS depression occurs depression of both facilitatory and inhibitory pathways leading to drowsiness ,disorientation and coma.

- Local anaesthetic agents block neuromuscular transmission when administered intra-arterially(formation of neurotransmitter, receptor and local anaesthetic complex which has negligible conductance).

b) Cardiovascular system (CVS): it binds specifically to myocardial proteins.In toxic concentrations,the drug decreases the peripheral vascular resistance and myocardial contractility producing hypotension and possibly cardiovascular collapse.

Routes of administration: topical, infiltration, intrathecal, epidural

Dose: 2mg/kg

Pharmacokinetics:

Absorption : The absorption of local anaesthetic agent is related to

1. The site of injection (Intercostals> epidural> brachial plexus> subcutaneous)
2. The dose linear relationship exists between the total dose and the peak blood concentration achieved.

Distribution: 95% protein bound in plasma. The volume of distribution is 47-103 litres.

Metabolism: occurs in liver by N-dealkylation primarily to pipcoloxylidine. N-desbutyl bupivacaine and 4-hyroxy bupivacaine are also formed.

Excretion : 5% of the dose is excreted in the urine as pipcolyloxylidine. 16% is excreted unchanged .The clearance is 0.47 L/min and the elimination half life (after intravenous administration) is 0.31-0.61 hours.

Pharmacodynamics: pKa of bupivacaine is 8.1. Heptane: Buffer partition coefficient is 27.5.

The onset and duration of conduction blockade is related to the pKa, lipid solubility and the extent of protein binding of the drug.

- A low pKa and high lipid solubility are associated with a rapid onset time.
- High degree of protein binding is associated with a long duration of action.

Toxicity /side effects:

i) Allergic reactions to amide type local anaesthetics- extremely rare

ii) Intravascular injection can cause refractory cardiac depression .

CLONIDINE

Clonidine hydrochloride is an imidazoline derivative with alpha 2-adrenergic agonistic activity and has a variety of different actions including antihypertensive effects as well as the ability to potentiate the effects of local anaesthetics.It can provide pain relief by an opioid-independent mechanism.

STRUCTURE:

PREPARATIONS : Oral - 0.1/0.25/0.3 mg tablets

Injections - clear colourless solution containing

0.15mg/ml of Clonidine Hydrocloride

Mechanism of action:

- Stimulation of inhibitory α_2- adrenoreceptors to reduce central neural transmission in the spinal neurons,thereby decreasing noradrenaline release from sympathetic nerve terminals and consequently decreasing sympathetic tone.

- Inhibition of substance P release is believed to be involved in the analgesic. Some contribution to the analgesic effect of clonidine may be through release of acetylcholine in the neuraxial region.

Pharmacological actions:

Cardiovascular system(CVS): when administered intravenously clonidine causes a transient increase in the blood pressure (due to stimulation of vascular α_1 receptors) followed by a sustained decrease. The heart rate and venous return may

decrease slightly; the drug has no effect on cardiac contractility and cardiac output is well maintained. The systemic vascular resistance is decreased with long term treatment.

Central Nervous System(CNS): clonidine decreases cerebral blood flow and intraocular pressure. It exerts a depressant effect on both spontaneous sympathetic outflow and afferent Aδ and C- fibre mediated somatosympathetic reflexes.

Autonomic system: clonidine decreases gastric and small bowel motility and is an antisialogogue.

Genitourinary system: clonidine reduces renovascular resistance ; however little alteration in the glomerular filtration rate occurs.

Pharmacokinetics:

Absorption: the drug is rapidly and well absorbed when administered orally; the oral bioavailability is 100%.

Distribution: clonidine is well lipid soluble and penetrates the central nervous system. The drug is 20% protein bound in the plasma; the volume of distribution is 1.7-2.5 L/kg.

Metabolism: less than half of an administered dose is metabolized in the liver to inactive metabolites.

Excretion: 65% of the dose of clonidine is excreted unchanged in the urine; some 20% is excreted in the faeces. The clearance is 1.9-4.3 ml/min/kg and the elimination half life is 6-23 hours. The latter is markedly increased in the presence of renal impairment; the dose of clonidine should be reduced if the glomerular filtration rate is < 10ml/min.

Toxicity / side effects: drowsiness, dry mouth, fluid retention, impotence and constipation. Rapid withdrawal of the drug may lead to life-threatening rebound hypertension and tachycardia.

USES:

- To prolong the duration of epidural/spinal anaesthesia
- Epidural add on agent for relief of severe cancer pain and intra - articular pain
- As anxiolytic
- For sedation

- To prevent &/or treat shivering

REVIEW OF LITERATURE

1. Epidural clonidine analgesia for intractable cancer pain.

Eisenach JC, et al in 1995,conducted a randomized control study in Eighty-five patients with severe cancer pain despite large doses of opioids or with therapy-limiting side effects from opioids. The patients were randomized to recieve 30 micrograms/h epidural clonidine or placebo for 14 days, together with rescue epidural morphine. Pain was assessed by visual analog score (VAS), McGill Pain Questionnaire, and daily epidural morphine use. Success was defined as a decrease in either morphine use of VAS pain, with the alternative variable either decreasing or remaining constant. Blood pressure, heart rate, and degree of nausea and sedation were monitored. Successful analgesia was more common with epidural clonidine (45%) than with placebo (21%). This was particularly prominent in those with neuropathic pain (56% vs. 5%). Pain scores were lower at the end of the treatment period in patients with neuropathic pain treated with clonidine rather than placebo, whereas morphine use was unaffected. Clonidine, but not placebo, decreased blood pressure and heart rate. Hypotension was considered a serious complication in 2 patients receiving clonidine and in 1 patient receiving placebo. This study confirmed the findings from previous animal studies which showed the

effective, potent analgesic properties of intraspinal alpha 2-adrenergic agonists and suggests that

epidural clonidine may provide effective relief for intractable cancer pain, particular of the neuropathic type.

2. Hemodynamic and analgesic profile after intrathecal clonidine in humans.

Filos.KS , et al in 1995, performed a study to evaluate the dose-response hemodynamic and analgesic profiles of intrathecal clonidine administered after a standard surgical intervention, without perioperative administration of additional analgesics, local anesthetics or tranquilizers. METHODS: In a randomized prospective double-blind study, 30 women who underwent elective cesarean section during general anesthesia with thiopental, nitrous oxide, and halothane were studied. Forty-five minutes after tracheal extubation, a lumbar intrathecal puncture was performed, and the patients received 150 (group 1), 300 (group 2), or 450 (group 3) micrograms clonidine. Postoperative analgesia was assessed on a visual analog scale at rest and after deep cough at standard time points up to 24 h. The results demonstrated the dose-dependent analgesia after intrathecal clonidine at doses as great as 450 micrograms. The nearly immediate analgesic effect observed after intrathecal injection of 300 and 450 micrograms clonidine strongly argues for a spinal rather than a systemic site of action of this alpha 2-adrenergic

agonist. After 300 and 450 micrograms intrathecal clonidine a relative hemodynamic stability is observed, suggesting a pressor effect at peripheral sites.

3. Spinal administration of alpha 2-adrenoceptor agonists and opioids or local anaesthetic agent.

Motsch J,et al in 1996, extensively studied the effects of combined spinal administration of alpha(2)-adrenoceptor agonists, local anaesthetics, and opioids. The motor and the sensory block of spinal and epidural anaesthesia is enhanced and prolonged by the combination of clonidine with the local anaesthetics lidocaine, tetracaine and bupivacaine. Because higher plasma levels of local anaesthetics were measured when clonidine was injected epidurally, the enhancement of the local anaesthetic's effect by clonidine is not due to slowed resorption, but rather to direct spinal and supraspinal effects of clonidine. Furthermore, direct local anaesthetic properties of clonidine on nerve fibres are discussed. Circulatory effects of combined clonidine and local anaesthetics are the result of the specific spinal blockade and the central and peripheral effects of clonidine. In humans, the interaction seems to be additive rather than supra-additive. Neither the incidence nor the severity of side effects is increased by a combined therapy with opioids. Despite the sedative properties of clonidine, there is no increased risk of respiratory depression when clonidine is given in

combination with opioids. The inhibiting effect on the sympathetic nervous system activity regularly observed during spinal administration of clonidine supports the value of this therapy and will support its use in the future. Therefore, the combination of alpha(2)-adrenoceptor

agonists with local anaesthetics or opioids is reasonable and may improve anaesthetic practice.

4. Epidural clonidine used as the sole analgesic agent during and after abdominal surgery.

De Cock Em , et al in 1997, investigated the analgesic potency of epidural clonidine when used as the sole analgesic agent during and after major abdominal surgery. Fifty young adult patients undergoing intestinal surgery under general anesthesia with propofol were studied. At induction, the patients received epidurally either an initial dose of 2 micrograms/kg clonidine followed by an infusion of 0.5 microgram/kg/h (group 1, n = 10) or 4 micrograms/kg followed by 1 microgram/kg/h (group 2, n = 20) or 8 micrograms/kg/h followed by an infusion of 2 micrograms/kg/h (group 3, n = 20). By this study they demonstrated that Epidural clonidine used as the sole analgesic agent provided dose-dependent control of the hemodynamic changes associated with surgical stimulation. It also produced dose-dependent postoperative analgesia without major side effects.

5. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials

Anthony Rodgers,et al in 2000 ,conducted a study to obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal

anaesthesia on postoperative morbidity and mortality. 141 trials including 9559 patients for which data were available before 1 January 1997. Trials were eligible irrespective of their primary aims, concomitant use of general anaesthesia, publication status, or language. Results: Overall mortality was reduced by about a third in patients allocated to neuraxial blockade (103 deaths/4871 patients versus 144/4688 patients, odds ratio=0.70, 95% confidence interval 0.54 to 0.90, P=0.006). Neuraxial blockade reduced the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59% (all P<0.001). There were also reductions in myocardial infarction and renal failure. Although there was limited power to assess subgroup effects, the proportional reductions in mortality did not clearly differ by surgical group, type of blockade (epidural or spinal), or in those trials in which neuraxial blockade was combined with general anaesthesia compared with trials in which neuraxial blockade was used alone. Conclusions: Neuraxial blockade reduces postoperative mortality and other serious

complications. The size of some of these benefits remains uncertain, and further research is required to determine whether these effects are due solely to benefits of neuraxial blockade or partly to avoidance of general anaesthesia. Nevertheless, these findings support more widespread use of neuraxial blockade.

6. Effects of Clonidine combined with small dose bupivacaine during spinal anaesthesia for inguinal herniorraphy

I.Dobrydnjov and H.Klockoff, et al in 2003, demonstrated the different actions of clonidine including the ability to potentiate the effects of local anaesthetics. 45 patients, ASA physical status I-II, age >20 yr, who underwent open inguinal herniorrhaphy as a day case procedure were recruited for the study. The following drug combinations were slowly injected intrathecally over 3 min. patients in Group B received 6 mg of bupivacaine in 8% glucose, patients in Group BC15 received 6 mg of bupivacaine in 8% glucose and 15µg of clonidine and patients in Group BC30 received 6mg of bupivacaine in 8% glucose and 30 µg of clonidine. All test solutions were diluted with saline to total volume of 3 ml. they concluded that the study has shown that the use of clonidine as adjuvant to small dose (6 mg) bupivacaine is effective for ambulatory inguinal herniorrhaphy. The addition of intrathecal clonidine 15µg or 30 µg to small dose bupivacaine increased the spread and duration of analgesia and produced an

effective spinal anaesthesia. Clonidine 15 μg combined with bupivacaine 6 mg in 8% glucose did not produce prolonged postoperative motor block and is therefore to be preferred for ambulatory inguinal herniorraphy.

7. Comparison Of The Verbal Rating Scale And The Visual Analog Scale For Pain Assessment

Randall C. Cork,et al in 2004, performed a survey to determine if the simple Verbal Rating Scale (VRS) could be substituted for the Visual Analog Scale (VAS) to measure pain intensity in chronic pain patients. Eighty-five (85) chronic pain patients were surveyed using both VAS and VRS. Pearson correlation coefficient($r = 0.906$) and p value (< 0.0001) showed excellent correlation between the two, although VRS showed a tendency to be higher than VAS ($p=0.068$). They proposed that the VRS provided a useful alternative to the VAS scores in assessment of chronic pain. Eighty-five consecutive chronic pain patients who presented at the Pain Management Service at Louisiana State University Health Sciences Center, Shreveport (LSUHSC-S) were surveyed. A physician interviewed the patient and filled out survey forms. Patients were asked to rate their pain with the VAS and the VRS. The VRS as described above is easily assessed, takes less time than the VAS, and can be performed without

the need of paper and pen. It is relatively simple to understand and thus provides a correlation which is more definitive than a distance mark. Their analysis took a measurement engineering approach by

looking at the reliability and validity of VRS, using VAS as the standard. Reliability is assessed with an analysis of correlation, while validity is assessed with Student's t-test for paired data. The VRS is a simple instrument that can save time and can be compared favorably to the VAS.

8. Epidural Clonidine for postoperative pain after Total Knee Arthroplasty: A Dose-Response Study.

Huang.Y,et al in 2007, conducted a randomized double-blind study to evaluate the optimal epidural dose of clonidine administrated after total knee arthroplasty (TKA) in Eighty adult patients. Methods: All the patients were randomly assigned to one of four study groups (C0, C1, C2, C4), 20 patients each. After surgery, group C1, C2 and C4 patients received patient-controlled epidural analgesia (PCEA) with morphine (0.1 mg/mL) and clonidine (1, 2, 4 μg/ mL, respectively) in 0.2% ropivacaine 100 mL, while group C0 patients received only PCEA morphine (0.1 mg/mL) and 0.2% ropivacaine for postoperative control. Pain relief was evaluated by the total PCEA consumption and visual analog scale. Systolic blood pressure (SBP), heart rate (HR), sedation, sensory

and motor blockade were also recorded during the 72 h postoperatively. The degree of knee flexion was also recorded daily until discharge. Results: Group C0, C1, C2 and C4 patients requested 71.8±19.5,

49.6±12.3, 48.1±9.3 and 39.4±9.0 mL respectively. Patients in the clonidine groups experienced less postoperative pain during the 72 hours after surgery. Discussion: The concentration of clonidine 1 μg/mL mixture with morphine and ropivacaine has to be considered the optimal epidural dose. The higher dose of epidural clonidine (4 μg/mL) produced the best analgesia but the degree of sedation and sensory blockade were more severe and longer lasting; it required careful monitoring of the patient.

9. Epidural fentanyl-bupivacaine compared with clonidine-bupivacaine for analgesia in labour

S. Kizilarslan, et al in 2006, demonstrated that Alpha-adrenergic agonists produce pain relief through an opioid independent mechanism and may be alternatives to opioids for combination with local anaesthetics for analgesia during labour. He studied 41 pregnant women. Epidural block was performed with 75 μg clonidine (n=20) or 50 μg fentanyl (n=21) combined with 0.125% bupivacaine (10 Ml). Maternal vital parameters were measured. Analgesia was evaluated using a visual analogue scale (VAS); sedation was scored using a five-

point scale. There were no differences in maternal vital parameters, fetal heart rate (FHR) or Apgar scores between the groups. Analgesia lasted longer in the bupivacaine-clonidine group (139.4±31 min) compared with the bupivacaine–fentanyl group (127.9±48 min) (P=0.42). Additional analgesic

requirement was more often in the fentanyl–bupivacaine group and total bupivacaine requirement was less in the clonidine–bupivacaine group (22.5±12.5mg vs. 30.9±12.8 mg) (P=0.04). This study confirmed that the combination of bupivacaine and clonidine provides satisfactory analgesia for first-stage labour, and of longer duration than bupivacaine–fentanyl.

10. Effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section

I.van Tuijl , et al in 2006, demonstrated that the addition of clonidine(75 μg) to hyperbaric bupivacaine prolongs the duration of spinal analgesia and reduces the need for postoperative self- administration of i.v.morphine after caesarean section by conducting a randomized controlled double-blind trial. The study was done in healthy women(ASA I or II) presenting for an elective caesarean section from a group of 209 candidates. Patients were randomly allocated to receive spinal anaesthesia using either bupivacaine 0.5% (2.2 ml) heavy with 0.5 ml normal saline 0.9% (total- 2.7 ml) (Group B) or bupivacaine 0.5% (2.2 ml) heavy with clonidine (75 μg) in 0.5 ml normal saline 0.9% (2.7

ml) (Group BC). Spinal anaesthesia was performed using a 25-gauge pencil point needle with the patient in the sitting position at the lumbar 3-4 interspace. They concluded that addition of 75 µg clonidine to hyperbaric bupivacaine prolongs spinal analgesia and the motor block after Caesarean section and

improves early analgesia. In this study, this effect was obtained without clinically relevant maternal or neonatal side effects.

11. Epidural clonidine added to a bupivacaine infusion increases analgesic duration in labor without adverse maternal or fetal effects

Robert K. Parker,et al in 2007, conducted a study to determine the potential for maximizing the time to first epidural supplement when adding clonidine to a 0.625 $mg \cdot ml^{-1}$ bupivacaine continuous epidural infusion following epidural fentanyl bolus in early labor for patients allowed to ambulate. Maternal and fetal effects secondary to clonidine were also evaluated. Methods : Sixty-eight laboring primigravid women received a 3-ml epidural test dose of lidocaine with epinephrine, followed by a fentanyl 100-µg bolus (in a 10 ml-volume). The patients then received a 0.625 $mg \cdot ml^{-1}$ bupivacaine continuous epidural infusion, either with or without clonidine (5 $\mu g \cdot ml^{-1}$), at a rate of 10 $ml \cdot h^{-1}$. Pain scores and side effects were recorded for each patient. Results : The overall quality of analgesia was similar in both groups. The mean duration prior to request for additional analgesia was significantly longer in the clonidine group (269 ± 160 min), compared to the control group (164 ± 64 min). No patient in either group

experienced any detectable motor block; one patient (clonidine group) complained of mild thigh

numbness and was not allowed to ambulate. While mean blood pressure was approximately 6 mmHg lower in the clonidine group at 1, 1.5, and 3.5 h, this was not clinically significant. No adverse effects on maternal heart rate or fetal heart rate were noted. Conclusion : In early laboring patients, addition of clonidine prolonged the analgesia duration of a 0.625 $mg \cdot ml^{-1}$ bupivacaine continuous epidural infusion following 100 μg epidural fentanyl (after a lidocaine-epinephrine test dose) without a clinically significant increase in side effects.

MATERIALS AND METHODS

Patient selection:

The study population consist of ASA I & ASA II patients in the age group of 18 years to 65 years admitted to undergo elective orthopaedic lower limb surgeries at Govt. Stanley Hospital, Chennai during the period of January 2008 to June 2008. After getting approval by the institutional ethical committee and after obtaining written informed consent from each patient ,the study was conducted.

Inclusion criteria:

1. Age Group 18 – 65 years
2. ASA I and ASA II
3. Elective orthopaedic lower limb surgeries
4. Duration of Surgery between 2:00 to 2:30 hours.

Exclusion criteria:

1. Patient refusal
2. Age < 18 years and age > 65years

3. ASA III and ASA IV

4. Patient posted for emergency surgery.

5. Ischemic heart disease/ rheumatic heart disease

6. Sinus bradycardia / heart blocks / conduction defects

7. Preoperative hypotension

8. Local infection at lumbar area

9. Pre-existing neurological disorders

10. Coagulation defects and patient on anticoagulants

Preoperative assessment:

- Routine clinical examination
- Biochemical investigations,
- Electrocardiogram and chest x-ray were examined thoroughly for the conduct of anaesthesia.

Conduct of anaesthesia:

Patients were allocated randomly into two equal groups (20 in each group).Group P (placebo) received 1 ml of normal saline with the first dose of

epidural 0.5% bupivacaine. Group C (clonidine) received 50µg of clonidine diluted with normal saline to 1 ml epidurally along with the first dose of bupivacaine.

No premedication was given. On arrival in the operating room, baseline cardiorespiratory parameters viz., Heart Rate(HR), Systolic blood pressure(SBP), Diastolic blood pressure(DBP),Mean arterial pressure(MAP) and Respiratory rate(RR) were recorded.

A good intravenous access was established using 18G IV cannula. Preloading was done with crystalloids (10 ml/kg).

With the patient in sitting posture, after informing the procedure to the patient & under strict aseptic precautions, epidural space was identified at L3-L4 interspace using 17G Tuohy needle by loss of resistance technique. 19G epidural catheter was threaded in a cephalad direction & 4 cm catheter length was kept inside the epidural space. A test dose of 3 cc of 1.5 % lignocaine with adrenaline (5 µg/ml) was given.After confirming negative result for test dose, epidural catheter was fixed and secured with tapes. A standard anaesthetic technique was followed in all patients.

Epidural 1st dose - 14 ml of 0.5% bupivacaine + 1ml of placebo or 50 μg of injection clonidine diluted with normal saline to 1 ml.

Epidural 2nd dose - 6ml of 0.5% bupivacaine (90 mins after 1st dose)

Patients with duration of surgery between 2-2:30 hours requiring standard 2 doses of epidural local anaesthetics were only taken up for study. Unanticipated prolonged duration of surgery (requiring more than 2 doses) were excluded from the study.

Time of incision was noted.

Intra-operatively the patient was monitored with ECG, BP and SpO2.

The following parameters were continuously monitored and noted every 10 mins:

1. Heart rate (HR)
2. Systolic blood pressure (SBP)
3. Diastolic blood pressure (DBP)
4. Mean arterial pressure (MAP)

5. Respiratory rate (RR)

- Ramsay sedation scale (RSS) was also noted every 30 min.

All patients were given oxygen supplementation (4-5 L/min) through Hudson's face mask. No intravenous opioid analgesics were supplemented during the study. Intravenous fluid management was done based on Mean arterial blood pressure and surgical blood loss.

RAMSAY SEDATION SCALE:

1. Patient is anxious and agitated or restless, or both.
2. Patient is co-operative, oriented and tranquil.
3. Patient responds to commands only.
4. Patient exhibits brisk response to light glabellar tap or loud auditory stimulus.
5. Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus.
6. Patient exhibits no response.

POST- OPERATIVE MONITORING :

The epidural catheter was retained in position. Postoperatively the patient was transferred to the Post Anaesthetic Care Unit(PACU) where PR,SBP ,DBP, SPO2 & RR monitored continuously and recorded every hour.

The intensity of pain was measured by using the verbal rating pain scale.

Pain Score (Verbal Rating Score):

Grade 0 - No complaint of pain

Grade 1 - Patient complaints of pain but tolerable (mild pain)

Grade 2 - Patient complaining of severe pain and demands relief

(Moderate pain)

Grade 3 - Patient restless and screaming with pain(Severe pain)

When the patient complained of pain , the pain intensity was assessed based on verbal rating scale & if pain score reaches 1, epidural top up of 6ml of 0.125% bupivacaine was given to the patient.

The time of first rescue analgesia(TFA) was calculated from the time of injection of study drug in the epidural space to the time when the verbal rating pain score reached 1 in the post-operative period.

Number of epidural top-ups (6 ml of 0.125% bupivacaine) required by

each patient for a period of 48 hours was noted in both the groups.

LIST OF ORTHOPAEDIC LOWER LIMB SURGERIES

S.NO	DIAGNOSIS AND SURGICAL PROCEDURES	NO. OF CASES	
		GROUP P	GROUP C
1.	Fracture shaft of femur- ORIF with interlocking nailing	**8**	**10**
2.	Fracture both bones leg- ORIF with intramedullary nailing	**6**	**5**
3.	Fracture neck of femur- Hemiarthroplasty	**3**	**2**
4.	Supracondylar fracture femur – ORIF with Dynamic Condylar Screw (DCS)	**2**	**3**
5.	Fracture Patella- ORIF with Tension Band Wiring	**1**	**-**
	TOTAL CASES	**20**	**20**

OBSERVATIONS

STATISTICS AND ANALYSIS:

Forty patients posted for orthopaedic lower limb surgeries of ASA I and ASA II were taken up for the study. They were allocated randomly into two equal groups of 20 each. Group P receieved 1 ml of placebo along with the first dose of epidural 0.5% bupivacaine and Group C received 50 μg of clonidine diluted with normal saline to 1 ml along with first dose of epidural 0.5% bupivacaine. A standard anaesthetic technique was followed in all patients. The patients were assessed by the same observer in the postoperative period.

All the data were expressed as mean ± standard deviation (SD). Qualitative variables were compared with 'Chi-square test' and quantitative variables were compared with 'the student 't' test'. The level of statistical significance was set at $P < 0.05$.

DEMOGRAPHIC PROFILE:

TABLE- 1-Comparison of age distribution

S.NO	PARAMETERS	GROUP		P VALUE
		GROUP P	GROUP C	
		MEAN ± SD	MEAN ± SD	
1.	Age (yrs)	40.60 ± 7.40	36.85 ± 9.59	P-0.183(NOT SIGNIFICANT)

Figure 1: BOX- PLOT compares the age distribution of GROUP P and GROUP C

The age distribution was comparable between the two groups, P value not significant.

TABLE – 2

SEX DISTRIBUTION

The P value for sex distribution is 0.695 – Not Significant.

FIGURE -2

SEX DISTRIBUTION

TABLE -3

Comparison of Height and Weight

S.NO	PARAMETERS	GROUP		P value
		GROUP P	GROUP C	
		MEAN±SD	MEAN±SD	
1.	HEIGHT(cms)	164.00±5.73	166.65±6.01	P-0.152(Not Significant)
2.	WEIGHT(kgs)	59.60±5.16	59.50±6.10	P-0.956(Not Significant)

FIGURE -3

HEIGHT AND WEIGHT

There was no significant difference in Height and Weight

between the two groups.

TABLE- 4

DURATION OF SURGERY

	GROUP P	GROUP C	P VALUE
			P – 0.359
DURATION OF SURGERY(HRS)	2.14 ± 0.07	2.12 ± 0.07	NOT SIGNIFICANT

There was no significant difference in the duration of surgery (hrs) between the two groups.

FIGURE -4

DURATION OF SURGERY (HRS)

TABLE- 5

HEART RATE

S NO.	PARAMETERS (MINUTES)	GROUP		P VALUE
		GROUP P	GROUP C	P<0.05-SIG
		MEAN ± SD	MEAN ± SD	
1.	HR PRE-OP	94.10 ± 11.81	97.05 ± 12.81	.441(NOT SIG)

2.	**HR10**	**92.20 ± 8.16**	**94.70 ± 11.69**	**.438(NOT SIG)**
3.	**HR20**	**88.90 ± 8.70**	**90.40 ± 12.12**	**.656(NOT SIG)**
4.	**HR30**	**85.95 ± 7.52**	**87.30 ± 11.77**	**.668(NOT SIG)**
5.	**HR40**	**84.80 ± 8.29**	**87.10 ± 12.81**	**.504(NOT SIG)**
6.	**HR50**	**83.85 ± 8.34**	**85.45 ± 13.03**	**.646(NOT SIG)**
7.	**HR60**	**82.75 ± 8.66**	**84.90 ± 11.79**	**.515(NOT SIG)**
8.	**HR70**	**81.95 ± 9.24**	**82.55 ± 10.73**	**.851(NOT SIG)**
9.	**HR80**	**82.35 ± 8.96**	**81.65 ± 9.9.52**	**.812(NOT SIG)**
10.	**HR90**	**83.00 ± 9.59**	**82.00 ± 11.94**	**.908(NOT SIG)**
11.	**HR100**	**84.55 ± 9.02**	**83.6 ± 10.51**	**.761(NOT SIG)**
12.	**HR110**	**86.30 ± 7.55**	**85.7 ± 10.26**	**.834(NOT SIG)**
13.	**HR120**	**84.15 ± 10.00**	**86.85 ± 10.21**	**.594(NOT SIG)**
14.	**HR130**	**87.30 ± 8.41**	**86.20 ± 10.28**	**.713(NOT SIG)**
15.	**HR140**	**87.00 ± 8.60**	**88.65 ± 11.08**	**.602(NOT SIG)**
16.	**HR150**	**90.70 ± 8.98**	**90.70 ± 10.53**	**1.00(NOT SIG)**

TABLE -6

SYSTOLIC BLOOD PRESSURE

S	**PARAMETERS**	**GROUP**	**P VALUE**

NO.	(MINUTES)	GROUP P	GROUP C	P<0.05- SIG
		MEAN ± SD	MEAN ± SD	
1.	SBP PRE-OP	128.80 ± 6.68	130.20 ± 6.47	0.505(NOT SIG)
2.	SBP 10	120.20 ± 11.70	118.65 ± 5.85	0.600(NOT SIG)
3.	SBP 20	110.05 ± 11.64	107.40 ± 10.88	0.462(NOT SIG)
4.	SBP 30	113.85 ± 13.51	112.70 ± 6.85	0.736(NOT SIG)
5.	SBP 40	114.90 ± 9.29	108.30 ± 22.37	0.231(NOT SIG)
6.	SBP 50	116.00 ± 8.57	111.05 ± 7.16	0.055(NOT SIG)
7.	SBP 60	115.70 ± 9.81	110.25 ± 5.98	0.041(SIG)
8.	SBP 70	116.00 ± 7.38	108.70 ± 8.97	0.008(SIG)
9.	SBP 80	114.80 ± 7.96	112.95 ± 7.51	0.454(NOT SIG)
10.	SBP 90	114.50 ± 7.04	111.80 ± 8.47	0.280(NOT SIG)
11.	SBP 100	113.65 ± 8.56	110.35 ± 7.88	0.212(NOT SIG)
12.	SBP 110	118.35 ± 5.38	112.45 ± 7.30	0.006(SIG)
13.	SBP 120	120.35 ± 5.33	113.75 ± 8.90	0.007(SIG)
14.	SBP 130	117.55 ± 5.05	113.00 ± 8.37	0.044(SIG)
15.	SBP 140	118.70 ± 6.34	114.80 ± 7.46	0.083(NOT SIG)
16.	SBP 150	124.10 ± 3.74	120.00 ± 8.03	0.045(SIG)

FIGURE – 5
HEART RATE

P-value is not significant among both the groups at any point of time during intra-operative heart rate monitoring.

FIGURE – 6
SYSTOLIC BLOOD PRESSURE

Systolic blood pressure monitoring between two groups were found to be insignificant except during 70, 110, 120, 130, 150 minutes.

TABLE – 7
DIASTOLIC BLOOD PRESSURE

S NO.	PARAMETERS (MINUTES)	GROUP		P VALUE P<0.05- SIG
		GROUP P	GROUP C	
		MEAN ± SD	MEAN ± SD	
1.	DBP PRE OP	82.40 ± 3.01	81.85 ± 4.93	0.673(NOT SIG)
2.	DBP 10	75.20 ± 8.70	74.00± 6.02	0.615(NOT SIG)
3.	DBP 20	68.15± 10.38	65.50 ± 10.18	0.420(NOT SIG)
4.	DBP 30	69.40 ± 9.63	69.15 ± 6.36	0.923(NOT SIG)
5.	DBP 40	71.60 ± 7.80	67.65 ± 15.14	0.306(NOT SIG)
6.	DBP 50	72.20 ± 8.35	68.70 ± 4.47	0.107(NOT SIG)
7.	DBP 60	73.20 ± 7.88	67.85 ± 3.74	0.009(SIG)
8.	DBP 70	72.55 ± 7.75	66.95 ± 5.60	0.013(SIG)
9.	DBP 80	71.75 ± 6.48	70.70± 4.95	0.568(NOT SIG)
10	DBP 90	72.65 ± 6.55	69.45 ± 4.87	0.088(NOT SIG)
11.	DBP 100	72.50 ± 7.49	69.85 ± 5.54	0.211(NOT SIG)
12.	DBP 110	74.30 ± 5.10	70.45 ± 4.42	0.015(SIG)

13.	**DBP 120**	**75.35 ± 6.67**	**71.85 ± 5.61**	**0.080(NOT SIG)**
14.	**DBP 130**	**73.30 ± 5.19**	**70.95 ± 5.07**	**0.156(NOT SIG)**
15.	**DBP 140**	**74.90 ± 6.20**	**71.65 ± 4.33**	**0.062(NOT SIG)**
16.	**DBP 150**	**79.15 ± 3.04**	**78.10 ± 4.61**	**0.401(NOT SIG)**

TABLE- 8

MEAN ARTERIAL PRESSURE

S NO.	PARAMETERS (MINUTES)	GROUP		P VALUE
		GROUP P	GROUP C	
		MEAN ± SD	MEAN ± SD	P<0.05- SIG
1.	MAP PRE OP	97.85 ± 3.51	97.90 ± 4.74	0.970(NOT SIG)
2.	MAP 10	90.40 ± 9.34	88.80 ± 5.61	0.516(NOT SIG)
3.	MAP 20	81.85 ± 10.05	78.85 ± 10.35	0.359(NOT SIG)
4.	MAP 30	83.85 ± 9.94	83.80 ± 5.52	0.984(NOT SIG)
5.	MAP 40	86.20 ± 8.15	84.65 ± 4.58	0.463(NOT SIG)
6.	MAP 50	86.70 ± 8.15	83.00 ± 4.66	0.086(NOT SIG)
7.	MAP 60	88.25 ± 8.97	82.05 ± 4.31	0.008(SIG)
8.	MAP 70	86.90 ± 7.38	80.85 ± 6.44	0.009(SIG)
9.	MAP 80	86.00 ± 6.58	84.70 ± 5.55	0.504(NOT SIG)
10.	MAP 90	86.40 ± 6.32	83.45± 5.77	0.132(NOT SIG)
11.	MAP 100	85.85 ± 7.76	83.65± 5.31	0.302(NOT SIG)
12.	MAP 110	89.35 ± 5.30	84.60 ± 5.04	0.006(SIG)
13.	MAP 120	89.80 ± 6.13	85.85 ± 6.22	0.050(NOT SIG)
14.	MAP 130	88.25 ± 4.35	85.05 ± 5.79	0.055(NOT SIG)
15.	MAP 140	88.90 ± 6.07	86.20 ± 4.80	0.127(NOT SIG)

16.	**MAP 150**	**94.00 ± 2.95**	**91.75 ± 5.15**	**0.098(NOT SIG)**

FIGURE -7

DIASTOLIC BLOOD PRESSURE

Intra-operative Diastolic Blood Pressure monitoring between the two groups were found to be insignificant except during 60, 70 and 110 minutes.

FIGURE -8

MEAN ARTERIAL PRESSURE

Intra-operative Mean Arterial Pressure monitoring between the two groups were found to be insignificant except during 60, 70 and 110 minutes.

TABLE- 9

RESPIRATORY RATE

S NO.	PARAMETERS (MINUTES)	GROUP		P VALUE P<0.05- SIG
		GROUP P	GROUP C	
		MEAN ± SD	MEAN ± SD	
1.	RR PRE OP	15.80 ± 1.58	19.75 ± 1.56	0.268(NOT SIG)
2.	RR 10	14.45 ± 1.47	15.20 ± 1.28	0.093(NOT SIG)
3.	RR 20	14.65 ± 1.87	15.10 ± 1.41	0.396(NOT SIG)
4.	RR 30	14.40 ± 2.37	14.55 ± 1.76	0.822(NOT SIG)
5.	RR 40	14.10 ± 2.04	14.30 ± 1.45	0.724(NOT SIG)
6.	RR 50	14.25 ± 1.58	14.30 ± 1.49	0.919(NOT SIG)
7.	RR 60	14.45 ± 2.01	14.45±1.27	1.000(NOT SIG)
8.	RR 70	14.55 ± 2.44	14.65 ± 1.27	0.872(NOT SIG)
9.	RR 80	14.70 ± 2.12	14.85 ± 1.35	0.792(NOT SIG)
10	RR 90	14.50 ± 1.76	14.35 ± 1.56	0.777(NOT SIG)
11.	RR 100	14.60 ± 1.50	14.35 ± 1.35	0.583(NOT SIG)
12.	RR 110	14.80 ± 1.73	14.40 ± 1.53	0.445(NOT SIG)
13.	RR 120	14.75 ± 2.07	14.80 ± 1.05	0.923(NOT SIG)
14.	RR 130	15.50 ± 2.91	15.00 ± 1.17	0.480(NOT SIG)
15.	RR 140	14.95± 1.47	14.90 ± 0.97	0.899(NOT SIG)
16.	RR 150	15.00 ± 1.45	15.05 ± 0.99	0.900(NOT SIG)

TABLE -10

RAMSAY SEDATION SCALE

TIME(min)	RSS		GROUP P	GROUP C	TOTAL
30	**1**	1. **COUNT**	**20**	**12**	**32**
		%WITH IN GROUP	**100%**	**60%**	**80%**
		2. **COUNT**	**0**	**8**	**8**
		%WITH IN GROUP	**0%**	**40%**	**20%**
60		1. **COUNT**	**20**	**0**	**20**
		%WITH IN GROUP	**100%**	**0%**	**50%**
		2. **COUNT**	**0**	**20**	**20**
		%WITH IN GROUP	**0%**	**100%**	**50%**
90		1. **COUNT**	**20**	**6**	**26**
		%WITH IN GROUP	**100%**	**30%**	**65%**
		2. **COUNT**	**0**	**14**	**14**
		%WITH IN GROUP	**0%**	**70%**	**35%**
120		1. **COUNT**	**20**	**19**	**39**
		%WITH IN GROUP	**100%**	**95%**	**97.5%**
		2. **COUNT**	**0**	**1**	**1**
		%WITH IN GROUP	**0%**	**5%**	**2.5**
150		**COUNT**	**20**	**20**	**40**
		%WITH IN GROUP	**100%**	**100%**	**100%**

According to Chi- square test, RSS was significant at 30 min (P-0.003), 60 min (P<0.001) and 90 min (P<0.001). RSS was not significant at 120 min and 150 min respectively.

FIGURE – 9

RESPIRATORY RATE

There was no significant difference in Respiratory rate between the two groups.

FIGURE -10

RAMSAY SEDATION SCALE

TABLE -11

VERBAL RATING SCALE

TIME IN HOURS	VERBAL RATING SCALE		GROUP P	GROUP C	TOTAL	CHI-SQUARE TEST
2		1. COUNT	18	20	38	P-0.487
		%WITH IN GROUP	90%	100%	95%	NOT SIG
	2	COUNT	2	0	2	
		%WITH IN GROUP	10%	0%	5%	
4		1. COUNT	0	19	19	P<0.001
		%WITH IN GROUP	0%	95%	47.5	SIG
	1	COUNT	16	1	17	
		%WITH IN GROUP	80%	5%	42	
	2	COUNT	4	0	4	
		%WITH IN GROUP	100%	100%	100%	
6		1. COUNT	6	8	14	P-0.741
		%WITH IN GROUP	30%	40%	35%	NOT SIG
		2. COUNT	14	12	26	
		%WITH IN GROUP	70%	60%	65%	
8		1. COUNT	0	4	4	P-0.072
		%WITH IN GROUP	0%	20%	10%	NOT SIG
		2. COUNT	19	16	35	
		%WITH IN GROUP	95%	85%	87.5%	
		3. COUNT	1	0	1	
		%WITH IN GROUP	5%	0%	2.5%	
12		1. COUNT	0	2	2	P<0.001
		%WITH IN GROUP	0%	10%	50%	SIG
		2. COUNT	7	18	25	
		%WITH IN GROUP	35%	90%	62.5%	
		3. COUNT	13	0	13	
		%WITH IN GROUP	65%	0%	32.5%	
18	1	COUNT	5	15	20	P-0.004
		%WITH IN GROUP	25%	75%	50%	SIG
		3. COUNT	15	5	20	
		%WITH IN GROUP	75%	25%	50%	
24	1	COUNT	1	11	12	P-0.001
		%WITH IN GROUP	5%	55%	30%	SIG
	2	COUNT	19	9	28	
		%WITH IN GROUP	95%	45%	70%	
36		2. COUNT	18	20	38	P-0.487
		%WITH IN GROUP	90%	100%	95%	NOT SIG
		3. COUNT	2	0	2	
		%WITH IN GROUP	90%	0%	5%	
48		1. COUNT	0	2	2	P-0.487
		%WITH IN GROUP	0%	10%	5%	NOT SIG
		2. COUNT	20	20	40	
		%WITH IN GROUP	100%	100%	100%	

FIGURE - 11

VERBAL RATING SCALE

The post-operative pain score(verbal rating scale) was found to be significantly low at 4, 12, 18 and 24 hours in Group C when compared to Group P. Significantly low pain scores were observed at 4, 12, 18 and 24 hours intervals in patients belonging to Group C($P < 0.001$ at 4 ,12 and 24 hours intervals and P -0.004 at 18 hours interval) than Group P as shown in figure-11. The study demonstrated that pain relief was significantly better ($P < 0.05$) in patients who received epidural bupivacaine with clonidine than the patients who received epidural bupivacaine with placebo.

TABLE -12

TIME OF FIRST RESCUE ANALGESIA

	GROUP		P VALUE
	GROUP P	GROUP C	
	MEAN ± SD	MEAN ± SD	
Time of first rescue analgesia(hrs)	3.27 ±0.53	6.05 ± 0.65	0.001 SIGNIFICANT

The mean time of first rescue analgesia (hours) was found to be (6.05±0.65 hours) in Group C than the (3.27±0.53 hours) observed in Group P which was statistically significant (P-0.001)

FIGURE- 12

TABLE -13

NO.OF POST OPERATIVE EPIDURAL TOP-UPS

The no of post operative epidural top ups were significantly low (4 or 5 doses) in group C compared to(6 or 7 doses) in group P.

FIGURE -13 - NO.OF POST OPERATIVE EPIDURAL TOP-UPS

DISCUSSION

Our knowledge of acute pain mechanisms has advanced sufficiently over the past decade so that rational rather than empirically derived therapy can be used by aiming specifically at interrupting the mechanisms responsible for the generation of clinical pain. Breakthrough pain after surgical procedures is now beginning to be recognized as constituting suboptimal management. This is an active research area. A number of clinical trials have been conducted to prove the efficacy of anti-nociceptive effect of α_2 agonists using different techniques and different types of

drugs with conflicting results. The use of epidural techniques also offer the advantage of effective prolonged postoperative analgesia as compared to nerve blocks and local infiltrations.

The dose-dependent antinociceptive effects of clonidine were demonstrated in 1981 (1). These effects are partly mediated by spinal cord muscarinic and nicotinic receptors and the release of acetylcholine and by the activation of inhibitory noradrenergic pathways (10). In experimental studies, animal models and clinical trials, subarachnoid opioids, local anesthetics and α_2 adrenergic agonists show synergistic or additive interactions (10,11). Intrathecal or epidural clonidine is not neurotoxic.

In this study, we found that bupivacaine and clonidine administered epidurally, reduced the amount of analgesic that patients required postoperatively suggesting that clonidine may enhance the analgesic effect of bupivacaine. This study correlates with the meta-analysis done by **Armand et al** (2) which concluded that epidural clonidine clearly produced an analgesic effect and reduced the need for other analgesics.

In this randomized control study, we have evaluated the analgesic efficacy of bupivacaine with clonidine mixture given through lumbar

epidural route in patient undergoing elective orthopaedic lower limb surgeries.

The level of sedation intraoperatively was monitored using Ramsay Sedation Scale. The patients in group C were well sedated and comfortable than in group P. This study correlates with the study conducted by **Antonio Mauro et al**(3) in which they concluded that the association of clonidine and local anaesthetic (ropivacaine) had produced longer analgesia and sedation.

Pain intensity was assessed using the verbal rating scale (VRS) post-operatively. Significant lower VRS scores after 2,4,6,8,12,18,24,26,48 hours has in group C demonstrated the clinical advantage of administering mixture of bupivacaine and clonidine through lumbar epidural route for effective postoperative analgesia.

Duration of analgesia was significantly more in group C patients receiving bupivacaine and clonidine mixture (6.05±0.64 hrs) as compared to group P (3.26±0.53 hrs). The demand for supplementary epidural top-ups over 48 hours postoperatively was significantly low in group C than group P. This correlates with the study of **Armand et al**(2).

Two patients of placebo group (10% of group P) and two patients of clonidine group (10% of group C) had episodes of hypotension with a

MAP< 70 mm Hg during intraoperative period who were managed with a single dose of ephedrine 6 mg iv and crystalloids , and this may be as a result of epidural bupivacaine as such. In the studies conducted by **Paech et al** (17) and **Senard et al**(21), they have concluded that epidural administration of clonidine caused a dose dependent reduction in haemodynamic parameters such as blood pressure and heart rate.

Postoperatively none of the patients had episode of hypotension. No incidence of any bradycardia was noted in both the group during intraoperative and postoperative period.

SUMMARY

This randomized control study was designed to evaluate the analgesic efficacy of bupivacaine with clonidine mixture given through lumbar epidural route for postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries and the quality of analgesia was compared with epidural plain bupivacaine.

Forty ASA I & II patients undergoing elective orthopaedic lower limb surgical procedure under epidural anaesthesia were randomly allocated into one of the two groups. Group P received 1 ml of normal saline along with first dose of

14ml 0.5% bupivacaine. Group C received 50 µg of clonidine diluted with normal saline to 1 ml along with the first dose of 14 ml 0.5% bupivacaine. Further top-up dose was given using 6 ml of 0.5 % bupivacaine, 90 min after the first dose. There was no complication encountered in technical skills in all forty patients.

Pain in the post-operative period was assessed using a verbal rating scale (VRS). Time of first rescue analgesic(TFA) and the supplementary analgesic doses required for 48 hours were noted for the two groups. Pain score were significantly less in Group C at 2,4,6,8,12,24,48 hours ($P < 0.05$) than in group

P. Overall pain score over 48 hours period also revealed better pain relief in group C ($P<0.05$) as compared to Group P.

Time of first rescue analgesic (TFA) in group C was significantly prolonged compared with group P . The postoperative analgesic consumption was also significantly less in group C than in group P. The incidence of hypotension did not differ significantly between the two groups & there was no bradycardia in both the groups.

So this study demonstrates that addition of clonidine to bupivacaine definitely improves the quality of analgesia by reducing the overall pain score, prolonging the duration of the time of first rescue analgesia and causing reduction of total analgesic consumption in the postoperative period without any hemodynamic instability.

CONCLUSION

1. Single dose administration of clonidine and bupivacaine mixture given through lumbar epidural route provides effective postoperative analgesia in patients undergoing elective orthopaedic lower limb surgeries, without any hemodynamic instability.

2. Epidural clonidine significantly reduces the postoperative analgesic consumption.

BIBLIOGRAPHY

1. **Alan N. Sandier:**The role of clonidine and alpha2-agonists for postoperative analgesia.CJA 1996/43:12/pp1191-4
2. **Antonio Mauro, et al.** Analgesia and sedation with epidural clonidine associated to 0.75% ropivacaine in the postoperative period of open cholecystectomy. Revista Brasileira de Anestesiologia [online]. 2003, v. 53, n. 5, pp. 586-590.
3. **Armand, et al**. M**et**a-an**al**ysis of the efficacy of extradur**al clonidine** to relieve postoperative pain: an impossible task. British Journ**al** of Anaesthesia, Vol 81, Issue 2 126-134, 1998 .
4. **Bock m,et al:** Comparison of caudal and intravenous clonidine in the prevention of agitation after sevoflurane in children.BJA.2002;88:790-6
5. **Carabine UA, Milligan KR Moore J**. Extradural clonidine and bupivacaine for postoperative analgesia. Br J Anaesth 1992; 68: 132-5.

6. **Christopherson R. Beattie C, Frank SM et al:** Perioperative morbidity in patients randomized to epidural or general anaesthesia for lower extremity vascular surgery: Anaesthesiology79:435,1993

7.

8. **De Kock, M., Gautier, P.** Epidural clonidine or bupivacaine as the sole analgesic agent during and after abdominal surgery: a comparative study. *Anesthesiology* **90**, 1354-62 (1999)

9. **De Negri, P. *et al*.** Spinal anesthesia with clonidine and bupivacaine in young humans: interactions and effects on the cardiovascular system. *Minerva Anestesiologica* **63**, 119-25 (1997)

10. **Dobrydnjov, I.,Axelsson, K:** Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine.Acta Anaesthesiologics Scandinavica,2002, vol 46,pp 806-814.

11. **Eisenach JC,et al.** Alpha2-adrenergic agonists for Regional Anaesthesia: A Clinical Review of Clonidine (1984-1995). Anaesthesiology .1996;85:655-674

12. **Gabriel JS and Gordin V.** Alpha 2 agonists in regional anaesthesia and analgesia. Curr Opin Anaesthesiol.2001;14:751-3

13.J.J.LEE and A. P. RUBIN: Comparis**on** of a **bupivacaine-clonidine** mixture **with** pla**in bupivacaine** for caudal analgesia **in** children.BJA, 1994, Vol. 72, No. 3 258-262

14.M . Serpell : **Anatomy, physiology and pharmacology of pain .** Anaesthesia & intensive care medicine , Volume 6 , Issue 1 , Pages 7 - 10

15.

16.NH Badner, R Bhandari and WE Komar:Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery.Canadian Journal of Anesthesia, Vol 41, 387-392

17.NH.Badner, et al. Bupivacaine 0.125% improves continuous postoperative epidural fentanyl analgesia after abdominal or thoracic surgery**.** Canadian Journal of Anaesthesia. 1994 May:387-92

18.Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. Anesthesiology 1990;73:853-9.

19.Paech, M. J., Pavy & Evans, S. F. Postoperative epidural infusion: a randomized, double-blind, dose-finding trial of clonidine in

combination with bupivacaine and fentanyl. *Anesthesia & Analgesia* **84**, 1323-8 (1997).

20. Peter Kranke, MD*, Leopold H. Eberhart: Single-Dose Parenteral Pharmacological Interventions for the Prevention of Postoperative Shivering.Anesth Analg 2004;99:718-727

21. Rodgers A, Walker N, Schug S: Reduction of post operative mortality and morbidity with epidural or spinal anaesthesia: Results from overview of randomised trials. BMJ 321:1493,2000

22. Ronald D .Miller, Miller's Anaesthesia, 6th edition, vol 2 : 2422-2426

23.

24. Senard, M. et al. Hemodynamic effects of epinephrine associated to an epidural clonidine-bupivacaine mixture during combined lumbar epidural and general anesthesia. Acta Anaesthesiologica Belgica, 49, 167-73 (1998)

25. Tran KM, et al. Intraarticular bupivacaine- clonidine- morphine versus femoral- sciatic nerve block in paediatric patients undergoing anterior cruciate ligament reconstruction. Anesth analg.2005;101:1304-10.

26. W. Klimscha and A. Chiari: Hemodynamic and Analgesic Effects of Clonidine Added Repetitively to Continuous Epidural and Spinal BlocksAnesth Analg 1995;80:322-7)

27. Yang CH,et al. Effect of intravenous clonidine on prevention of postepidural shivering. Ma Zui Xue Za Zhi.1993;31:121-6

28. Yuan-Shiou Huang, MD*, Liu-Chi Lin: Epidural Clonidine for Postoperative Pain After Total Knee Arthroplasty: A Dose“Response Study Anesth Analg 2007;104:1230-1235

PROFORMA

Name	:		Height	:
Age	:	Sex:	Weight	:
I.P.No	:		Diagnosis	:
ASA Status	:		Surgery	:
Group	:		Duration of surgery	:

Time of injection of drugs: Epidural I dose-
Dose of Clonidine or Placebo-

Epidural 2nd dose-

Time of incision-

INTRA
– OPERATIVE VITALS MONITORING

Time interval (minutes)

Sl. No	Parameter	Pre-op	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150
1.	HR																
2.	SBP																
3.	DBP																
4.	MAP																
5.	RR																
6.	RSS																

Intra–operative events:

POST–OPERATIVE MONITORING

Parameter	Time interval(hours)							
	2 hrs	4 hrs	6 hrs	8 hrs	12 hrs	18 hrs	24 hrs	48 hrs

1.**Pain Score:**
(Verbal Rating Scale)
0 – No Pain
1 – Mild Pain
2 – Moderate Pain
3 – Severe Pain

2.**Adverse Effects:**
Hypotension
Bradycardia

POST–OPERATIVE ANALGESICS CONSUMPTION

1. **Time of First Rescue analgesic:**

(TFA in hours)

2. **No.of Supplementary epidural top-ups required:**

(for 48 hours)